support a *prima facie* case of obviousness, there must be a suggestion or motivation to combine the reference teachings. M.P.E.P. § 2142. This fundamental tenet of patent law has been reflected in the holdings of a large number of Federal Circuit cases. For example, in reversing the Board of Appeals' affirmation of an obviousness rejection, the Federal Circuit recently stated that "because we do not discern any finding by the Board that there was a suggestion, teaching, or motivation to combine the prior art references cited against the pending claims, the Board's conclusion of obviousness, as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). In another case in which the Federal Circuit reversed a Patent Office determination of obviousness based on a combination of references, the court stated that "the examiner must show reasons that the skilled artisan, confronted with the same problem as the present inventors and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet* 149 F.3d 1350, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998). Moreover, as is stated in § 2143.01 of the M.P.E.P., the fact that references can be combined does not render the resultant combination obvious, in the absence of a suggestion of the desirability of the combination. As is discussed below, the rejection in this case does not meet these standards in supporting a *prima facie* case of obviousness and, thus, the rejection should be withdrawn.

In response to applicants' earlier statement that Hodgson does not teach the use of glycosaminoglycan analogs to increase transfection efficiency, the Advisory Action states that Dyer (not Hodgson) was relied upon for teaching the use of such analogs, rendering applicants' argument moot. The Advisory Action also states that glycosaminoglycan-induced viral-specific transfection is precisely what is novel about Dyer and the reason why this reference is relied upon. Applicants respectfully disagree, because in order for Dyer to be properly combined with

the cited other references, there must be some suggestion or motivation for one of skill in the art to do so, and applicants submit that there was not. Indeed, the teachings of the Dyer reference itself show that those of skill in the art would not have been motivated to combine its teachings with references that purport to provide a teaching of the transfection of normal cells, such as those that occur *in vivo*, for the reasons discussed below.

The specificity of the results of Dyer is due to their use of mutant cells that lack cell surface glycosaminoglycans, and Dyer's use of these cells also is of great significance in determining whether a connection can be made between the teachings of Dyer and any *in vivo* applications that may be suggested by the other references. As will become clear from the following discussion, there is a good reason why Dyer does not include a suggestion to use dextran sulfate as a *trans* receptor *in vivo*, and this is because the teachings of Dyer do not provide any indication that it would have a positive effect on transfection *in vivo* and, in fact, the teachings of Dyer are to the contrary.

For example, on page 196, Dyer states that dextran sulfate is not covalently linked to the host cell surface, and further states that this "is likely to severely compromise its ability to stabilize HSV-1 virions that collide with the cell surface." This statement alone forms a very firm basis for the conclusion that *in vivo*, in the context of naturally occurring, anchored glycosaminoglycans, exogenously administered dextran sulfate may not have an effect.

To add to this, applicants note that the authors of the Dyer paper themselves state that the effects of dextran sulfate may not be detectable in cells that display heparan sulfate on the their surfaces (i.e., normal cells *in vivo*; page 197). Also, the fact that Dyer states that dextran sulfate binds to sog9 cells in a saturable manner (page 196) provides additional support for the position

that in an *in vivo* context, in which cells contain cell surface anchored glycosaminoglycans, it may very well be that dextran sulfate may not have an effect.

Finally, applicants note that Dyer states that it was well established that dextran sulfate normally inhibits infection of cells by enveloped viruses (page 197, lines 1-6). The Examiner did not find this statement to be persuasive when pointed out in applicants' previous reply, because the Examiner states that Dyer made this statement as a context to explain why their results, observation of glycosaminoglycan-induced transfection, were surprising. Applicants respectfully disagree. By this statement, Dyer did not contradict what was known to happen with normal cells that contain glycosaminoglycans (i.e., that dextran sulfate normally inhibits infection of cells by enveloped viruses), but rather contrasted what they observed with mutant cells that lack glycosaminoglycans with what happens in normal cells. As the Examiner stated, use of the mutant cell line enabled investigation of the mechanism of glycosaminoglycan-facilitated entry but, as is discussed above, Dyer provides no basis for believing that exogenously added glycosaminoglycans would have any effect *in vivo*, with cells that contain anchored glycosaminoglycans, and indeed teaches to the contrary.

Thus, even if Dyer was not cited for teaching *in vivo* use, the teaching away discussed above supports the point that one of skill in the art would not have been motivated to combine the cited references. Therefore, even if one skilled in the art had by chance encountered Dyer in looking for a basis for varying an *in vivo* method (e.g., that suggested by Hodgson), a thorough reading of Dyer would reveal that the teachings of Dyer should not be considered for this purpose.

Hodgson, as discussed in previous replies, describes characterization of the effects of cationic lipids on retroviral transfection of cultured cells. Hodgson does not even mention

dextran sulfate for use in any purpose, not to mention enhancing viral uptake by cells *in vivo*. Thus, a suggestion to use dextran sulfate *in vivo* certainly does not come from Hodgson. In addition, all of the experiments of Hodgson are carried out in cultured cells. Thus, Hodgson does not even show that the compound they use (cationic lipids) is effective *in vivo*, not to mention provide evidence that a different compound could be effective in such a context.

Neither of the other cited references provides any basis for combining the teachings of references to support this rejection. The focus of Mislick, for example, is methods involving increasing or decreasing glycosaminoglycan levels in plasma or the cell surface to impact the level of transfection of polynucleotides. The other reference cited in this rejection, Marasco, describes the use of lentivirus vectors, such as HIV vectors, for use in gene expression studies, and nowhere suggests or provides motivation to enhance viral infectivity *in vivo* by use of a compound such as dextran sulfate.

Thus, because none of the cited references, alone or in combination, suggests or provides motivation to carry out the claimed methods, applicants respectfully request that the rejection under § 103(a) be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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